



0420 2459-1-003CIP #9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Zhou, Ming-Ming et al.
SERIAL NO. : 09/784,553 EXAMINER : Not Yet Assigned
FILED : February 16, 2001 ART UNIT : Not Yet Assigned
FOR : METHODS OF IDENTIFYING MODULATORS OF
BROMODOMAINS

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage in an envelope addressed to the ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231 on April 7, 2003.

Anne M. Jones

(Name of Person Depositing Mail)

Anne M. Jones 4/7/03.
(Signature and Date)

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Dear Sir:

Please enter the following amendments into the present application.

IN THE DRAWINGS:

Please delete Figure 13-1 through 13-13 without prejudice or disclaimer.

IN THE SPECIFICATION:

Please substitute the following amended paragraph for the paragraph on page 10, lines 19-25:

In a preferred embodiment the compound is selected by performing rational drug design with the set of atomic coordinates obtained from one or more of Tables 1-5 and 10-14. More preferably the selection is performed in conjunction with computer modeling. Compounds selected by these methods are also part of the present invention. Preferably the compound is a small organic molecule. More preferably the compound is an analog of acetyl-lysine. Even more preferably, the compound is not included in Table 15-1 to 15-33.

Please substitute the following amended paragraph for the paragraph starting on page 10, line 25 and ending on page 11, line 19:

The present invention also provides methods of identifying a compound that modulates the stability of the binding complex formed between P/CAF and Tat that is acetylated at the lysine residue at position 50 of SEQ ID NO:45. In one such embodiment the method comprises contacting the bromodomain of P/CAF or a fragment thereof with a binding partner in the presence of the compound under conditions in which the bromodomain of P/CAF and the binding partner bind in the absence of the compound. The stability of the bromodomain of P/CAF and the binding partner is then determined (e.g., measured). When there is a change in the stability of the binding complex between the bromodomain of P/CAF and the binding partner in the presence of the compound, the compound is identified as a modulator. In one embodiment of this type the binding partner is Tat that is acetylated at the lysine residue at position 50 of SEQ ID NO:45. In a preferred embodiment the binding partner is a fragment of Tat comprising an acetyl-lysine at position 50. In still another embodiment the binding partner is an analog of the fragment of Tat comprising an acetyl-lysine at position 50. When the stability of the bromodomain of P/CAF for the binding partner increases in the presence of the compound, the compound is identified as a stabilizing agent, whereas when the stability of the bromodomain of P/CAF for the binding partner decreases in the presence of the compound, the compound is identified as an inhibitor of the Tat-P/CAF complex. In a preferred embodiment the compound is selected by performing rational drug design with the set of atomic coordinates obtained from one or more of Tables 1-5 and 10-14. More preferably the selection is performed in conjunction with computer modeling. Compounds identified by these methods are also part of the present invention. Preferably the compound is an analog of acetyl-lysine. More preferably the compound is a small organic molecule not included in Table 15-1 to 15-33.

Please substitute the following amended paragraph for the paragraph starting on page 11, line 27 and ending on page 12, line 2:

Another aspect of the present invention provides methods of preventing, and/or retarding the progression and/or treating HIV infection in an individual. One such method employs administering to the individual compounds that modulate the Tat-P/CAF complex selected by performing rational drug design with the set of atomic coordinates obtained from one or more of Tables 1-5 and 10-14. In a preferred embodiment the compound administered is an acetyl-lysine

analog. In a particular embodiment this compound is a small organic molecule contained in Table 15-1 to 15-33. Preferably the compound either de-stabilizes or inhibits the Tat-P/CAF complex.

Please substitute the following amended paragraph for the paragraph on page 16, line 19 through line 24:

Figure 12 depicts the chemical structure common to the acetyl-lysine analogs of the present invention. R_1 , R_2 , and R_3 can be H, CH_3 , a halogen (*e.g.*, F, Cl, Br, I etc.), OH, SH, or NH_3^+ . R_4 can be an alkyl (including a peptide/protein attached thereto such as a peptide comprising an acetyl-lysine in which the "N" of the structure depicted is the epsilon nitrogen (*i.e.*, N^ϵ) of a lysyl residue), or an aryl group. *See also* Table 15-1 to 15-33 for examples.

Please delete line 26 on page 16.

Please substitute the following amended paragraph for the paragraph on page 20, line 11 through line 25:

The present invention provides the first detailed structural information regarding a bromodomain and a bromodomain complexed with its acetylated binding partner. The present invention therefore provides the three-dimensional structure of the bromodomain and a bromodomain acetylated binding partner complex. Since the interaction of the bromodomain with a histone for example, can play a significant role in chromatin remodeling/regulation, the structural information provided herein can be employed in methods of identifying drugs that can modulate basic cell processes by modulating the transcription. In a particular embodiment, the three-dimensional structural information is used in the design of a small organic molecule for the treatment of cancer or as disclosed below, HIV-1 infection and/or AIDs. In addition, the present invention provides a critical structural feature for a class of inhibitors (acetyl-lysine analogs) of the interaction between bromodomains and their protein binding partners which contain an acetylated-lysine (*e.g.*, Tat with P/CAF), *see* Figure 12, as well as a compilation of compounds that share this critical feature, *see* Table 15-1 to 15-33.

Please substitute the following amended paragraph for the paragraph on page 24, line 25 through line 28:

As used herein the term "acetyl-lysine analog" is used interchangeably with the term "analog of acetyl-lysine" and is a compound that contains the acetyl-amine-like structure as depicted in Figure 12. Examples of acetyl-lysine analogs are included in Table 15-1 to 15-33.

Please substitute the following amended paragraph for the paragraph on page 44, line 11 through line 17:

Initially a potential drug could be obtained by screening a random peptide library produced by recombinant bacteriophage for example, [Scott and Smith, *Science*, **249**:386-390 (1990); Cwirla *et al.*, *Proc. Natl. Acad. Sci.*, **87**:6378-6382 (1990); Devlin *et al.*, *Science*, **249**:404-406 (1990)] or a chemical library. In particular, based on the NMR structural analysis provided herein, compounds that comprise an "acetyl-amine-like" structure as depicted in Figure 12 are particularly good candidates. Examples of such "acetyl-lysine analogs" are included in Table 15-1 to 15-33.

Please substitute the following amended paragraph for the paragraph starting on page 55, line 28, through line 4 on page 56:

According to the invention, the component or components of a therapeutic composition, *e.g.*, an agent of the invention that interferes with the bromodomain-acetyl-lysine binding complex such as the peptide having the amino acid sequence of SEQ ID NOs:4, 5, 6, 46, or 47, or an acetyl-lysine analog as defined by Figure 12 and exemplified in Table 15-1 to 15-33, and a pharmaceutically acceptable carrier, may be introduced parenterally, transmucosally, *e.g.*, orally, nasally, or rectally, or transdermally. Preferably, administration is parenteral, *e.g.*, via intravenous injection, and also including, but is not limited to, intra-arteriole, intramuscular, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial administration.

Please insert Table 15-1 to 15-33, attached hereto as Table 15-1 through 15-33, into the specification after page 83 and before the claims.

IN THE CLAIMS:

Please cancel claims 37 through 43 without prejudice or disclaimer.

Please substitute the following amended claims for the original claims having the same claim number:

29. (Amended) A compound that is a small organic molecule identified by the method of Claim 28; wherein said compound is an analog of acetyl-lysine, but with the proviso that the compound is not included in Table 15-1 to 15-33.

34. (Amended) A compound that is a small organic molecule identified by the method of Claim 33; wherein said compound is an analog of acetyl-lysine, but with the proviso that the compound is not included in Table 15-1 to 15-33.

35. (Amended) An agent that can modulate the binding of P/CAF and Tat; wherein said agent is an analog of acetyl-lysine, but with the proviso that the agent is not included in Table 15-1 to 15-33.

REMARKS

Claims 1-43 are pending. Claims 37-43 have been cancelled without prejudice or disclaimer. Claims 29, 34 and 35 have been amended. Thus, claims 1-36 remain under consideration.

The amendments to the specification and claims were rendered to clarify aspects of the invention. Table 15-1 to 15-33 presents identical data to that originally included in Figure 13, which has now, accordingly, been deleted. No New Matter has been added by way of these amendments.

A Petition for Correction of Inventorship is attached herein in accordance with 1.48(b). This correction is respectfully requested in light of the claims cancelled by way of this amendment.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attachment is captioned "Version with markings to show changes made."

Conclusion

Examination on the merits is respectfully requested.

Respectfully submitted,



Veronica Mallon, Ph.D.
Agent for Applicants
Registration No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601

Date: April 7, 2003

Attachment: Table 15-1 to 15-33

Petition for Correction of Inventorship

VERSION WITH MARKINGS TO SHOW CHANGES MADE**IN THE SPECIFICATION:**

The following amended paragraph will replace the original paragraph on page 10, lines 19-25:

In a preferred embodiment the compound is selected by performing rational drug design with the set of atomic coordinates obtained from one or more of Tables 1-5 and 10-14. More preferably the selection is performed in conjunction with computer modeling. Compounds selected by these methods are also part of the present invention. Preferably the compound is a small organic molecule. More preferably the compound is an analog of acetyl-lysine. Even more preferably, the compound is not included in [Figure 13] Table 15-1 to 15-33.

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is selected by performing rational drug design with the set of atomic coordinates obtained from one or more of Tables 1-5 and 10-14. More preferably the selection is performed in conjunction with computer modeling. Compounds identified by these methods are also part of the present invention. Preferably the compound is an analog of acetyl-lysine. More preferably the compound is a small organic molecule not included in [Figure 13] Table 15-1 to 15-33.

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Line 26 on page 16 has been deleted:

[Figure 13 depicts examples of acetyl-lysine analogs. **[PRIOR ART]**]

The following amended paragraph will replace the original paragraph on page 20, line 11 through line 25:

The present invention provides the first detailed structural information regarding a bromodomain and a bromodomain complexed with its acetylated binding partner. The present

invention therefore provides the three-dimensional structure of the bromodomain and a bromodomain acetylated binding partner complex. Since the interaction of the bromodomain with a histone for example, can play a significant role in chromatin remodeling/regulation, the structural information provided herein can be employed in methods of identifying drugs that can modulate basic cell processes by modulating the transcription. In a particular embodiment, the three-dimensional structural information is used in the design of a small organic molecule for the treatment of cancer or as disclosed below, HIV-1 infection and/or AIDs. In addition, the present invention provides a critical structural feature for a class of inhibitors (acetyl-lysine analogs) of the interaction between bromodomains and their protein binding partners which contain an acetylated-lysine (e.g., Tat with P/CAF), see Figure 12, as well as a compilation of compounds that share this critical feature, see [Figure 13] Table 15-1 to 15-33.

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IN THE CLAIMS:

The following claims have been amended to replace the original claims having the same claim number:

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34. (Amended) A compound that is a small organic molecule identified by the method of Claim 33; wherein said compound is an analog of acetyl-lysine, but with the proviso that the compound is not included in [Figure 13] Table 15-1 to 15-33.

35. (Amended) An agent that can modulate the binding of P/CAF and Tat; wherein said agent is an analog of acetyl-lysine, but with the proviso that the agent is not included in [Figure 13] Table 15-1 to 15-33.

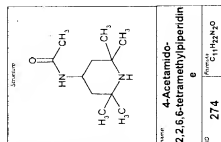
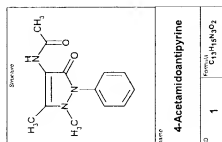
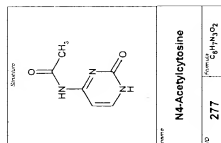
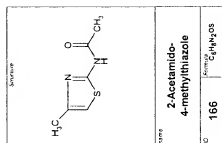
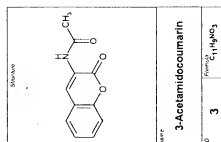
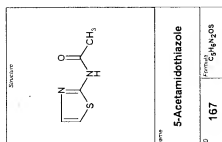
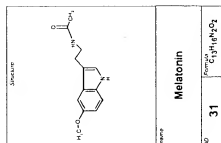
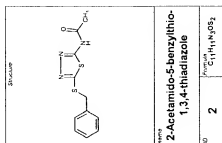
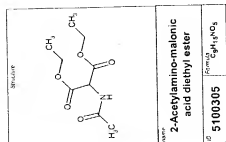
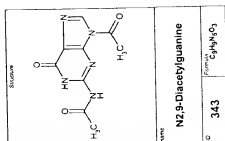
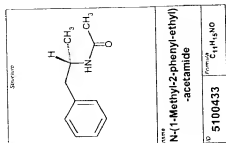
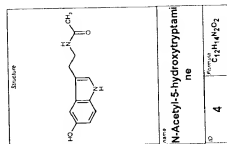
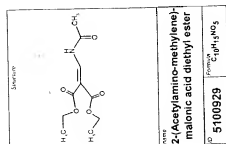
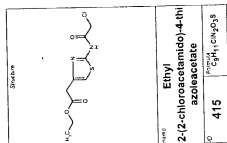
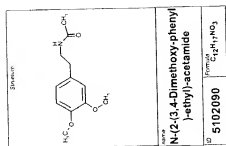
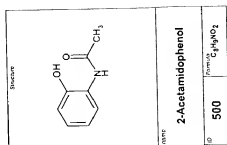


TABLE 15 - 1



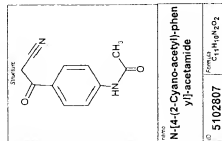
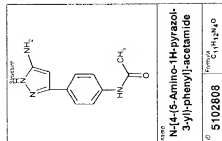
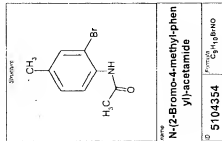
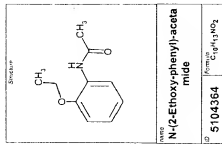
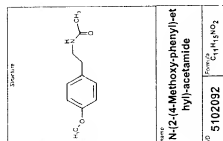
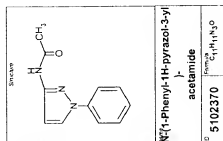
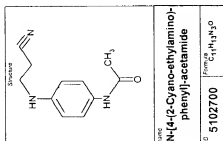
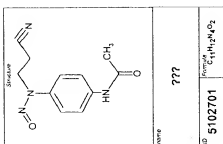


TABLE 15 - 3

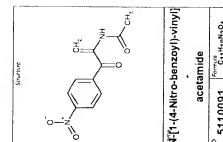
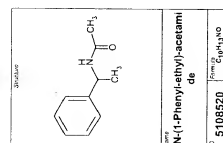
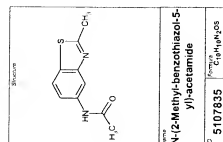
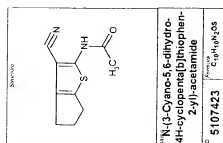
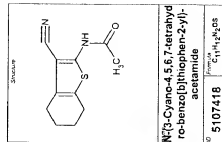
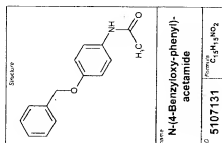
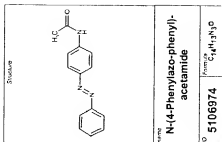
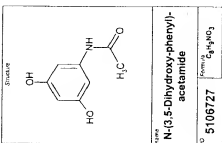


TABLE 15 - 4

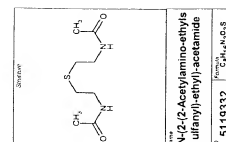
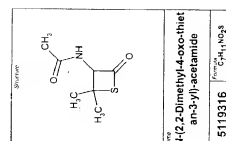
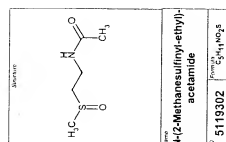
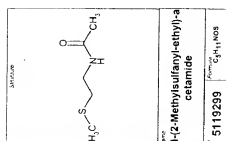
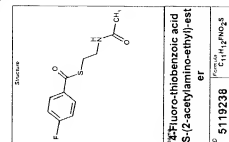
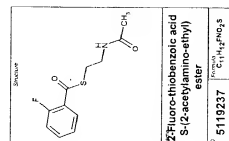
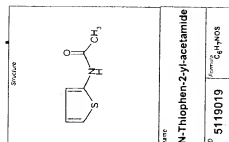
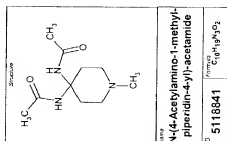


TABLE 15 - 5

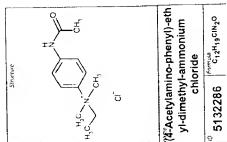
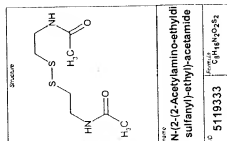
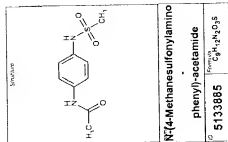
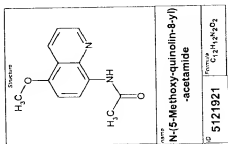
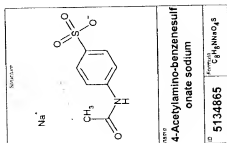
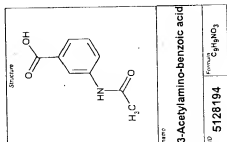
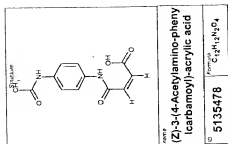
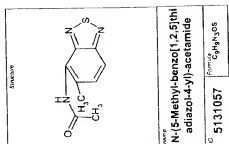


TABLE 15 - 6



09703554 044204

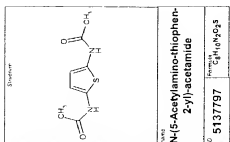
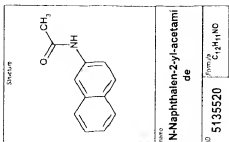
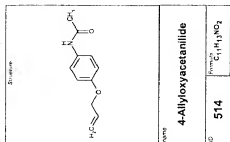
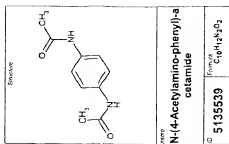
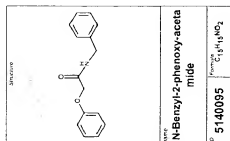
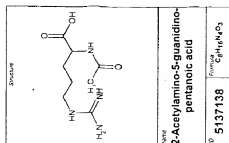
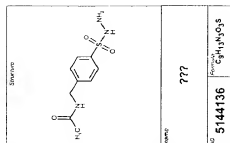
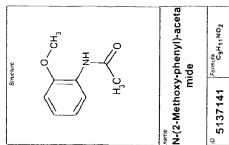


TABLE 15 - 7



09704159 = 041403

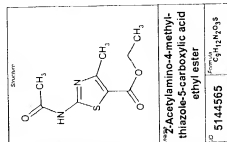
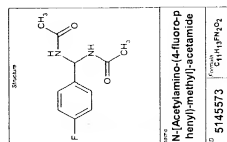
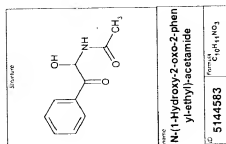
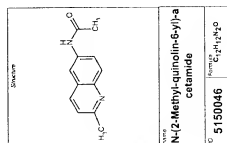
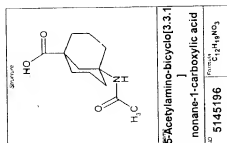
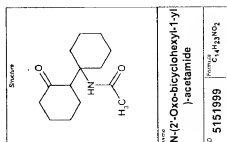
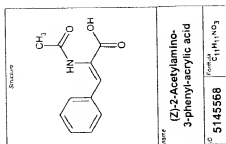
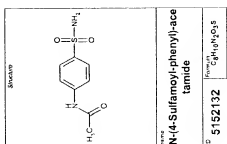


TABLE 15 - 8

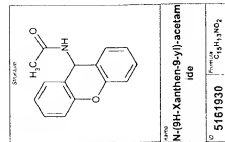
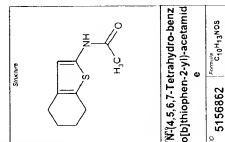
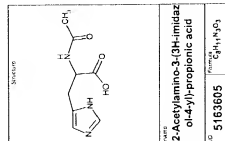
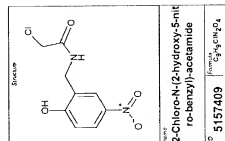
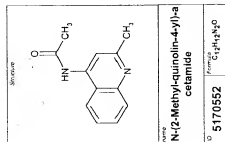
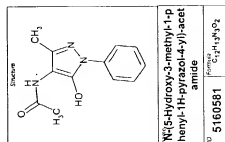
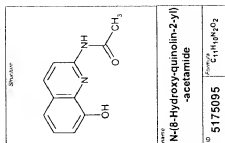
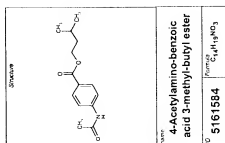


TABLE 15 - 9

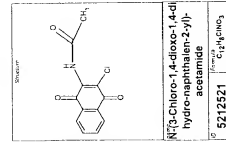
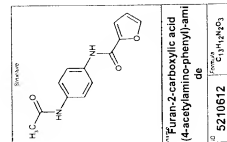
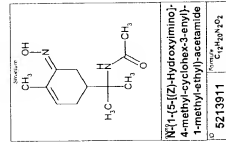
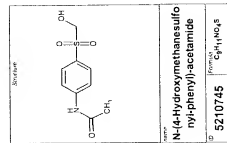
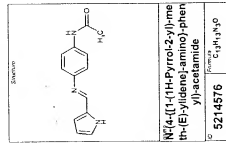
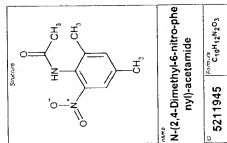
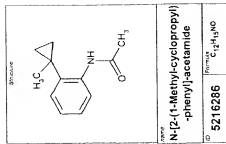
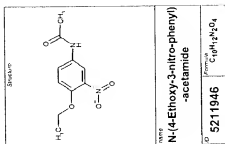


TABLE 15 - 11

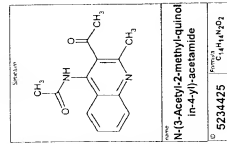
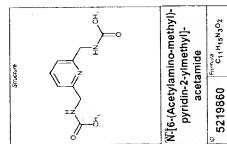
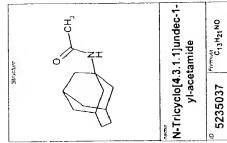
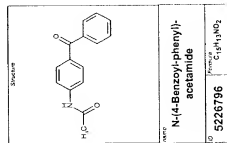
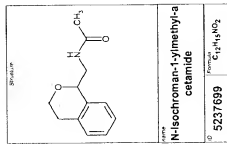
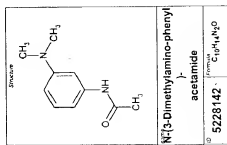
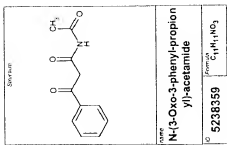
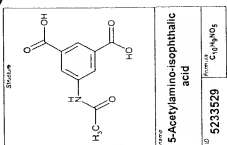
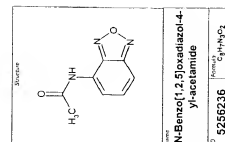
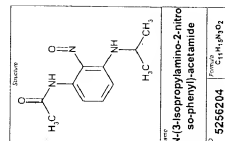
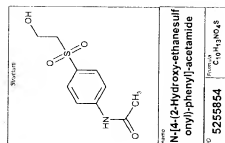
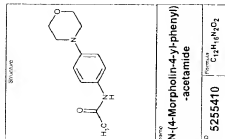
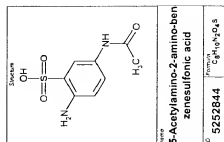
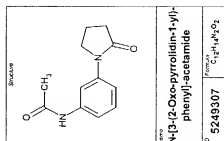
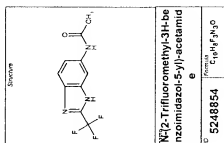
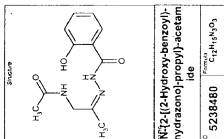
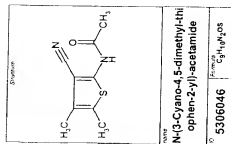
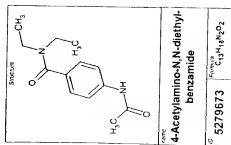
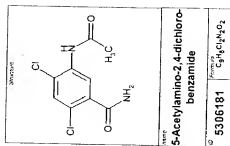
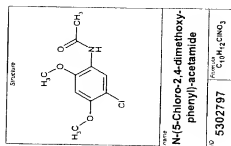
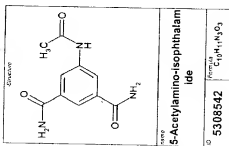
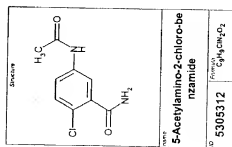
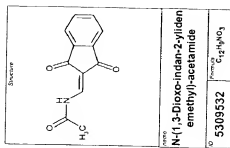
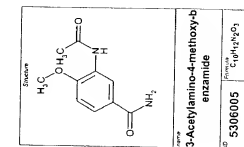


TABLE 15 - 12





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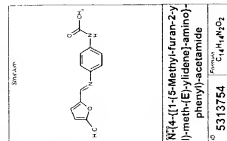
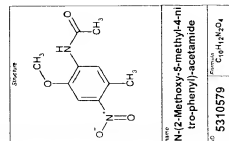
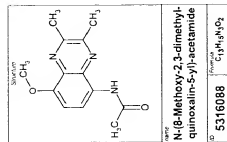
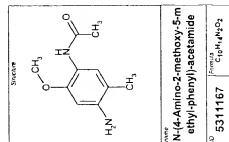
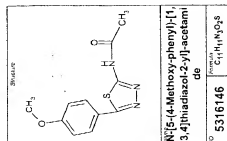
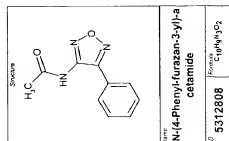
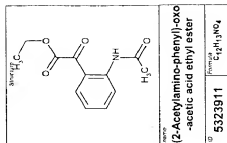
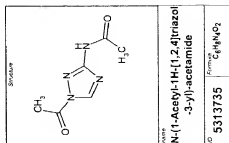


TABLE 15 - 16



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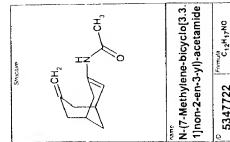
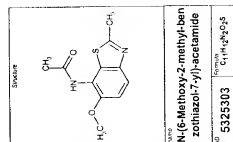
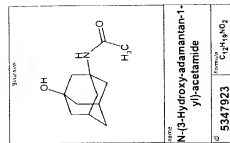
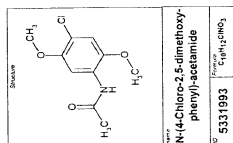
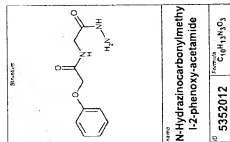
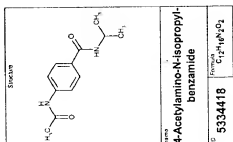
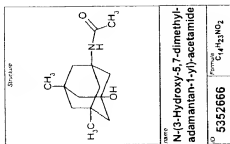
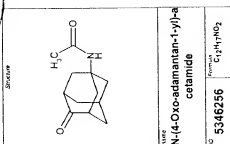


TABLE 15 - 17

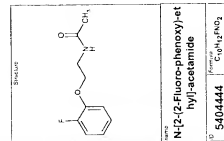
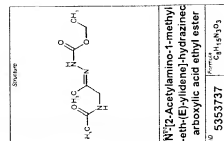
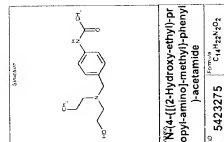
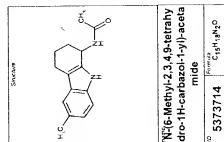
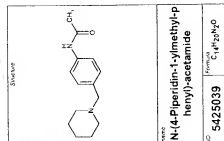
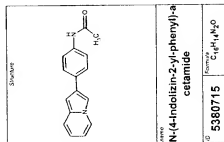
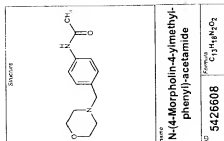
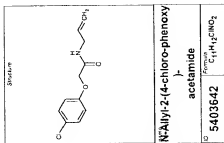


TABLE 15 - 18

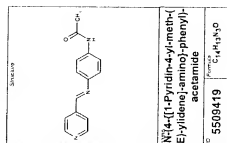
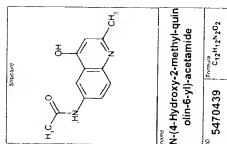
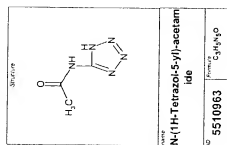
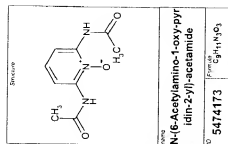
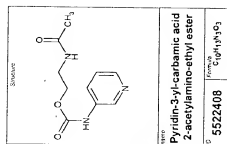
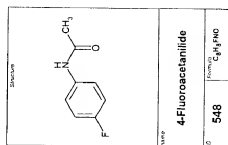
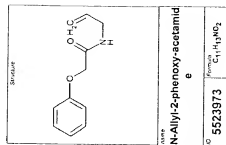
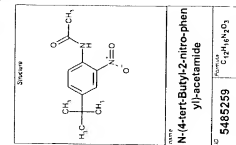


TABLE 15 - 19

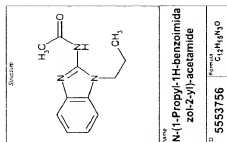
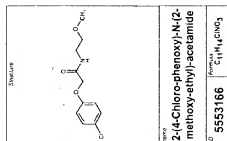
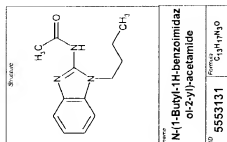
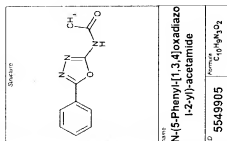
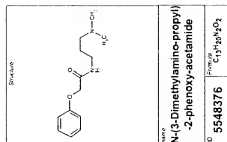
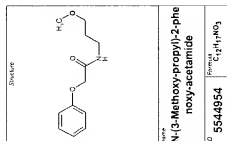
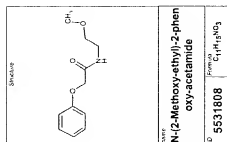
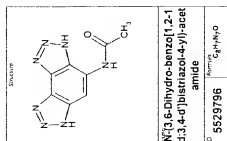


TABLE 15 - 20

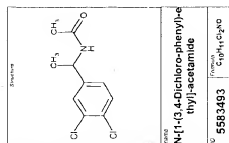
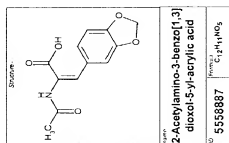
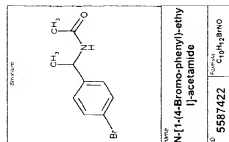
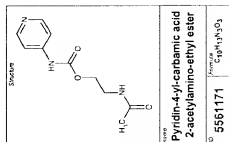
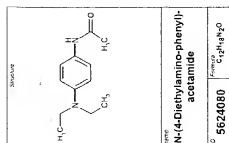
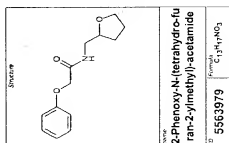
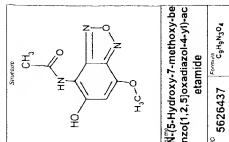
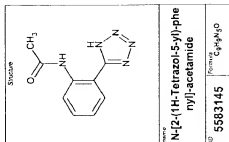
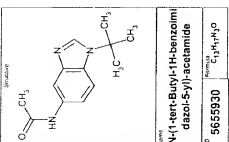
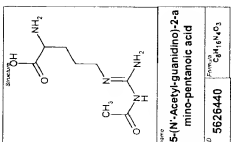
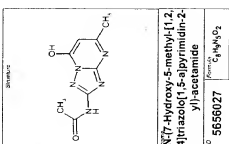
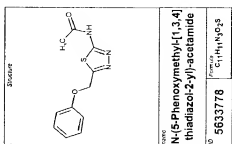
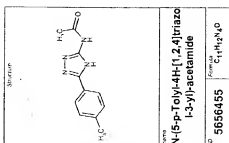
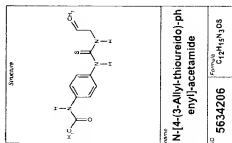
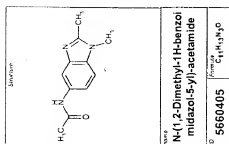
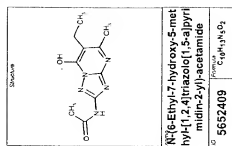


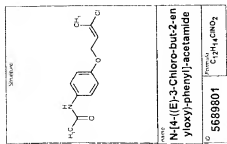
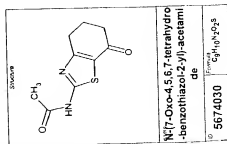
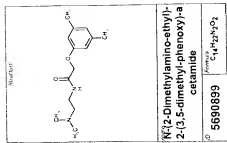
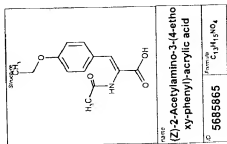
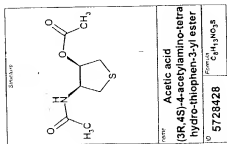
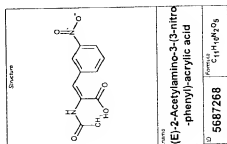
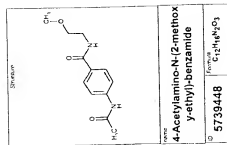
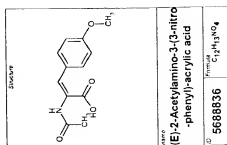
TABLE 15 - 21

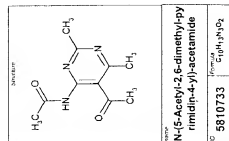
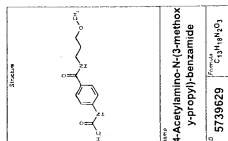
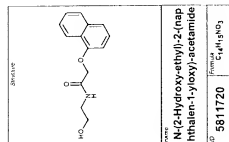
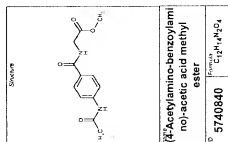
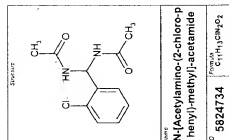
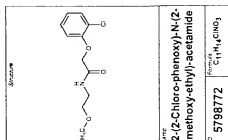
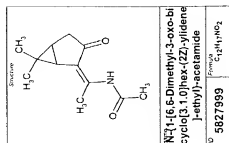
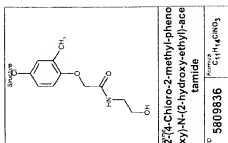


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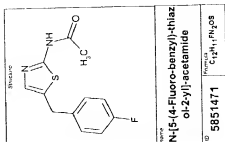
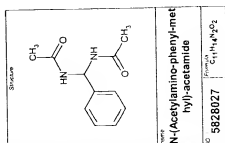
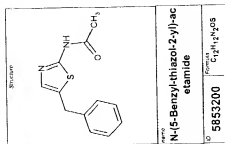
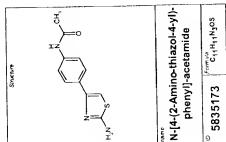
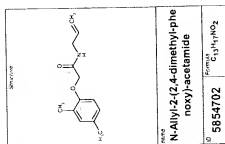
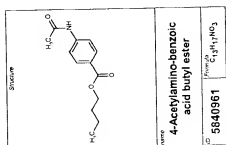
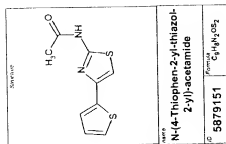
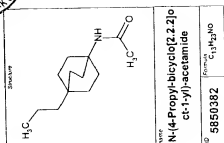


TABLE 15 - 25

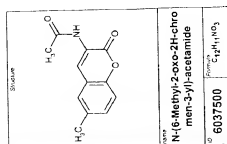
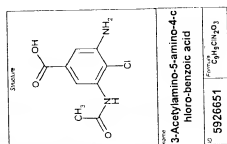
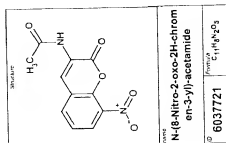
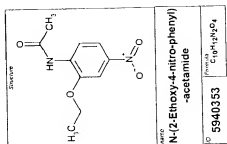
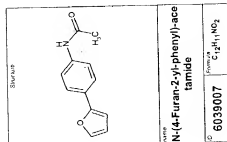
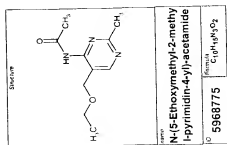
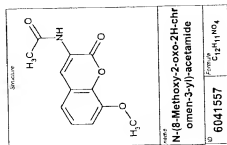
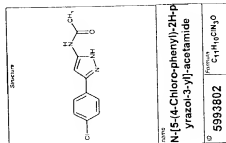


TABLE 15 - 26

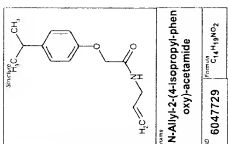
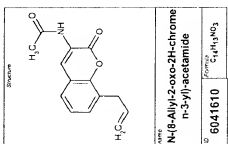
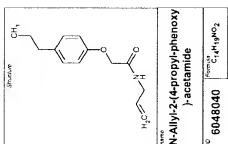
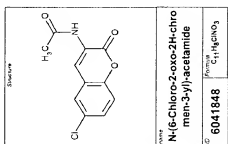
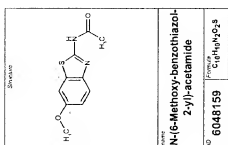
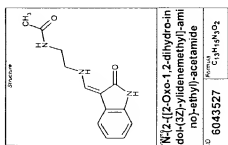
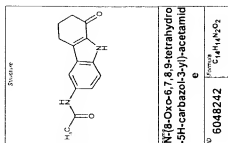
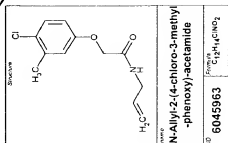


TABLE 15 - 27



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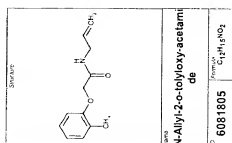
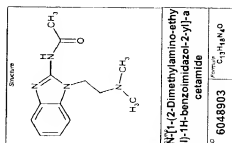
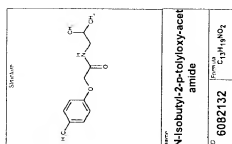
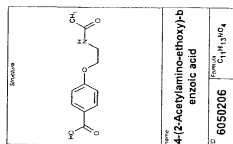
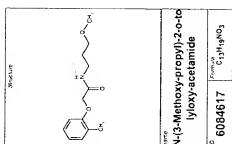
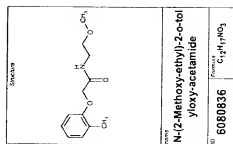
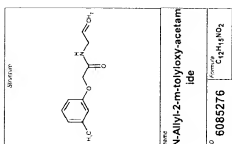
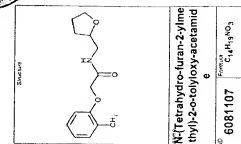
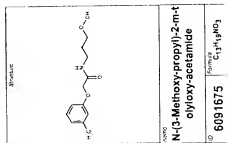
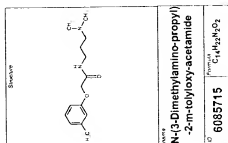
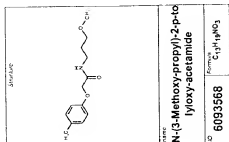
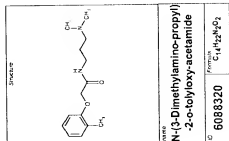
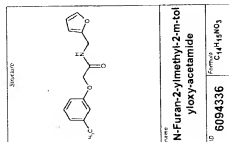
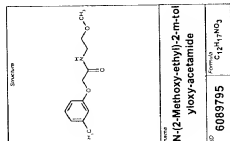
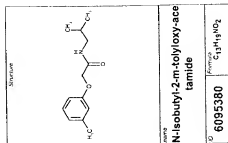
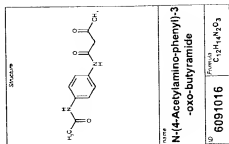


TABLE 15 - 28



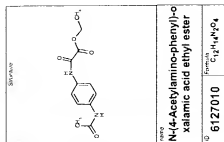
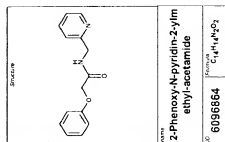
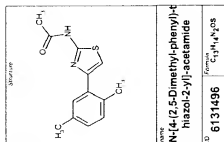
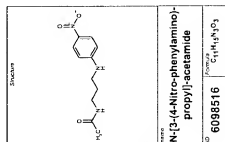
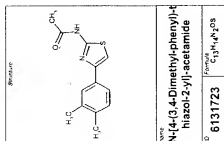
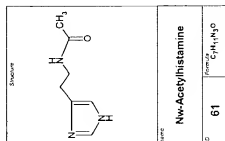
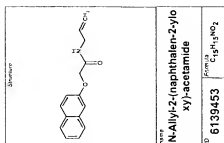
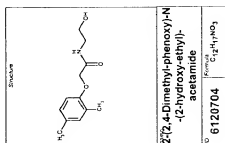


TABLE 15 - 30

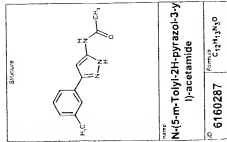
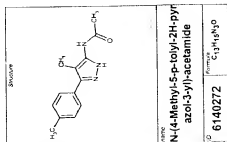
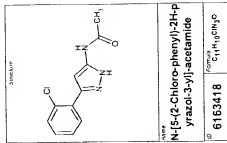
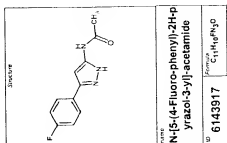
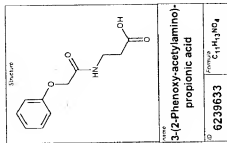
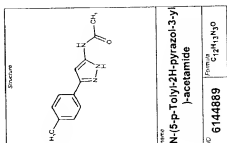
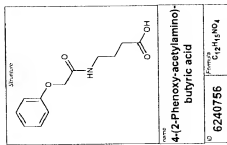
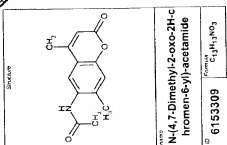


TABLE 15 - 31

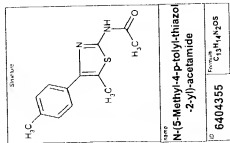
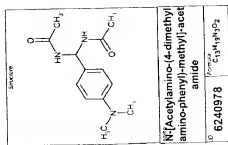
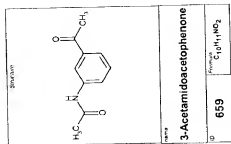
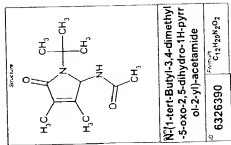
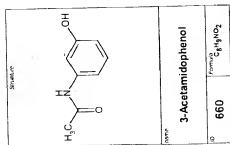
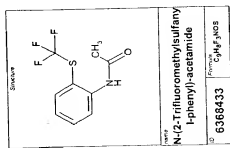
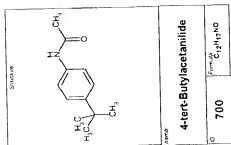
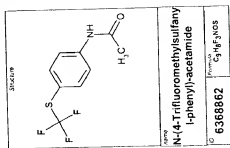


TABLE 15 - 32



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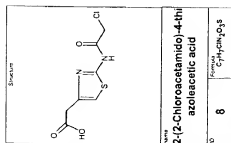


TABLE 15 - 33